ABSORPTION OF DRUGS

Peter G. Welling
University of Strathclyde, Glasgow, Scotland

INTRODUCTION

In the first edition of this encyclopedia the section on absorption covered a range of topics that included discussion of the cell membrane, parenteral and enteral absorption, clinical factors, and pharmacokinetic characterization of absorption.

During the intervening time many of these areas have changed, some more than others. There also have been changes in emphasis, reflected particularly in the rapidly expanding interest and discoveries in membrane penetration, exploitation of various dosage routes, formulation factors, and absorption enhancers.

Emphasis in this section will reflect these activities. In order to conserve space, the pharmacokinetic treatment of drug absorption has been omitted.

OBJECTIVES OF DRUG ABSORPTION

Absorption may be defined as the process by which a compound penetrates one or more biological membranes to gain entry into the body. Absorption is not to be confused with bioavailability, which describes entry of administered compounds into the systemic circulation. For some drugs and dosage routes, absorption and bioavailability may be identical, i.e., after intravenous (IV) dosing. However, in many cases they are not. For a drug that does not undergo any metabolic transformation between an immediate postabsorption site and entry into the systemic circulation, absorption and bioavailability are likely to be the same. All of the absorbed drug enters the systemic circulation. This is regardless of any drug that may be degraded or changed in some other way, i.e., preabsorption.

On the other hand, for any drug that is degraded at a point between the postabsorption site and entry into the systemic circulation, the systemic availability—bioavailability—will be less than the absorption. An orally administered drug that undergoes extensive first-pass hepatic clearance may give rise to poor oral bioavailability despite being efficiently absorbed from the gastrointestinal (GI) tract into the splanchnic circulation.

The pharmacologic activity profile of a systemically active drug is a function of its intrinsic activity and of the concentration profile that is achieved in the circulation. The speed of onset of action and the intensity and duration of activity are functions of the drug concentration profile.

The speed of onset of drug action is determined by the rate of drug absorption. Extreme cases are the use of bolus IV injection, which yields immediate and usually maximal pharmacologic effect, and slow controlled release, not necessarily by the oral route, where the onset of action is deliberately prolonged to achieve a desired therapeutic profile.

The intensity of pharmacologic effect is generally a function of the concentration of drug achieved in the circulation. Actual pharmacokinetic/pharmacodynamic relationships are often complex, but it is reasonable to generalize that higher circulating drug concentrations yield greater effect.

The levels of circulating drug that are achieved are a function of dose, absorption efficiency, overall bioavailability, distribution, and also clearance. The major determinant of drug distribution volume is its lipophilicity. As lipophilicity increases, so does the ability of the drug to cross biological membranes and move into extravascular environments, particularly into fatty tissue and the central nervous system (CNS).

Many drugs bind to plasma proteins, in particular to plasma albumin. Although binding of drugs to plasma proteins is dynamic and reversible, any drug that is bound at a particular time is necessarily confined to the plasma volume and thus cannot participate in extravascular distribution.

The last factor affecting circulating drug levels is clearance. The faster a drug is cleared from the circulation as a result of metabolism or any other process (i.e., the shorter its elimination half-life) the lower are its circulating levels. High circulating levels are less likely to be achieved with a high clearance drug than with a low clearance drug, and accumulation of a high clearance drug in the circulation with repeated dosing is unlikely.

Thus, the phenomenon of drug absorption is only one, albeit an important one, of several factors that determine

a drug profile in the circulation. It is important to understand all of these factors before drug profiles, and in particular pharmacokinetic/pharmacodynamic relationships, can be fully characterized, particularly in a predictive sense.

All of the above factors are functions of the physical and chemical properties of a drug. While distribution and clearance are affected only by drug properties and cannot generally be altered except by introducing some kind of interaction, drug absorption and bioavailability are often markedly influenced by route of administration, dosage form, and coadministration of other substances. Some of the major thrusts of pharmaceutical research during the last two decades have been devoted to these latter issues.

DOSAGE ROUTES

A required drug absorption profile is achieved by a variety of dosage routes. These routes may be divided into parenteral and enteral. Due to of the importance of the various routes of administration in drug delivery, and of recent advances in optimizing route-dependent drug delivery, they are briefly reviewed here.

PARENTERAL ROUTES

Parenteral delivery routes are those that do not give rise to drug absorption into the splanchnic circulation. Thus, they avoid the possibility of hepatic first-pass metabolism. It should be noted that some parenteral routes do not avoid other first-pass metabolism effects (e.g., pleural metabolism for some inhaled drugs). Some major parenteral drug delivery routes are intra-arterial, intrathecal, intravenous, intramuscular, transdermal, intranasal, buccal, inhalation, intraperitoneal, vaginal, and rectal.

Intra-arterial

Intra-arterial injection is used to deliver drugs directly to organs, for example, in cancer chemotherapy, and in the use of vasopressin for GI bleeding. Intra-arterial carmustine is effective to treat brain tumors (1) and pelvic intra-arterial actinomycin D is used for malignant trophoblastic disease (2).

Intra-arterial drug administration has potential safety implications. Embolization, arterial occlusion, and localized drug toxicity have been reported.

Intrathecal

Injection directly into the cerebrospinal fluid (CFS) ensures complete CNS bioavailability for drugs that cannot cross the blood-brain barrier. This dosage route is used to treat serious CNS infections such as meningitis and ventriculitis, and with such agents as mepivacaine and prilocaine for spinal anesthesia. Drugs injected intrathecally initially distribute into approximately 140 ml of CSF, thus producing high concentrations in the CNS with low risk of systemic toxicity.

Intravenous (IV)

IV administration introduces drug directly into the venous circulation. The shape of the resulting circulating drug profile is determined by the size, rate, and duration of injection. IV bolus is used for immediate therapeutic effect, typically for general anesthesia and for treatment of cardiac arrhythmia. IV dosing is popular for preclinical testing of compounds during drug development and also as a standard to determine absolute bioavailability from other dosage routes.

Intramuscular (IM)

Following intramuscular (IM) administration, drugs must cross one or more biological membranes in order to enter the systemic circulation. Intramuscular injection is used mainly for drugs and vaccines that are not absorbed orally, for example, aminoglycosides, insulin, and hepatitis vaccine. The IM route is often used for sustained medication and specialized vehicles, such as aqueous suspensions, oily vehicles, complexes and microencapsulation, which has been developed for slow delivery of drugs by this route (3).

Transdermal

Since the introduction of transdermal scopolamine (4), many transdermal delivery systems have been developed for systemic activity. Major advantages claimed for this drug delivery route include continuous release of drug over a specified period, low presystemic clearance, facile drug withdrawal by simply removing the device, and good patient convenience and compliance.

Some disadvantages relate to barrier properties of the skin, skin reactions, and the relatively large dose size. Transdermal delivery is a realistic option only for drugs generally given in small doses (<10 mg) and which have good membrane penetration. Drugs currently approved for transdermal delivery include clonidine, estradiol, nicotine, nitroglycerin, and scopolamine.

Intranasal

Intranasal administration may be used for local or systemic effects. Local effects include treatment of nasal allergies, rhinitis, and nasal congestion. Nasal delivery for systemic effects is established for a small number of drugs and is being examined for many others.

The sophisticated structure and specialized function of airways and membranes in the nasal cavity, and also the small surface area of this region, may limit its capacity for drug delivery. The effect of chronic drug exposure on the integrity of nasal membranes must also be considered. This problem may be compounded by the evident need for surfactants to achieve good systemic penetration with this dosage route.

Notwithstanding these factors, the physical characteristics of compounds for optimal intranasal absorption are the same as for other absorption routes. The drug must dissolve in the fluids of the nasal mucosa and must be sufficiently lipophilic to cross the membranes of the nasal epithelium. Nasal absorption is facilitated by the high permeability of small venules and capillaries associated with the nasal mucusa.

A variety of delivery systems have been described for nasal drug delivery, including drops, aerosols, nebulizers, and soluble matrices (5).

Small peptide molecules seem to be ideally suited for intranasal drug delivery. Vasopressin analogues and oxytocin are commercially available for intranasal dosage. Thyrotropin-releasing hormone agonists and antagonists, other vasopressin analogs, and peptides are being examined. Intranasal delivery of sex hormones has produced interesting results in animals. Intranasal delivery of insulin has been examined, but only with moderate success.

Buccal

Early recognition of buccal and sublingual absorption was manifested in the use of nitroglycerin by these dosage routes to treat severe headache and to relieve angina pectoris.

Drugs can be absorbed from the oral cavity itself or sublingually. Absorption from either route is rapid, sublingual more so apparently because of greater permeability of sublingual membranes and rich blood supply. The mean pH of saliva is approximately 6 so that drug absorption, predominantly passive in nature, is favored for unchanged molecules, acids with pK_a values >3, and bases with pK_a values <9.

Compounds that are currently marketed or are being considered for buccal or sublingual routes include organic nitrates, barbiturates, papaverine, trypsin, prochlorperazine, benzodiazepines, buprenorphine, captopril, isoprenalin, oxytocin, and nifedipine. Oxytocin is currently the only peptide marketed in sublingual form. Sublingual steroids have been examined with moderate success.

Inhalation

When a substance is inhaled, it is exposed to membranes of the mouth or nose, pharynx, trachea, bronchi, bronchioles, alveolar sacs, and alveoli (Fig. 1). The lung has a potential absorption surface of some 70 m^2, a much larger surface than the small intestine. However, the lungs and their associated airways are designed to deny access of administered compounds to the highly absorptive peripheral lung surfaces. The system is designed to deny access to particulate matter. However, if compounds can reach the peripheral region of the lung, absorption can be very efficient.

Particle (droplet) size and velocity of application control the extent to which inhaled substances penetrate into airway spaces. Optimum size for deep airway penetration is 3–5 μM. Large particles tend to deposit in upper airways.

Most inhalation devices deliver approximately 10% of the administered dose to the lower respiratory tract. A number of devices have been developed to increase lung delivery, and delivery of up to 21% has been

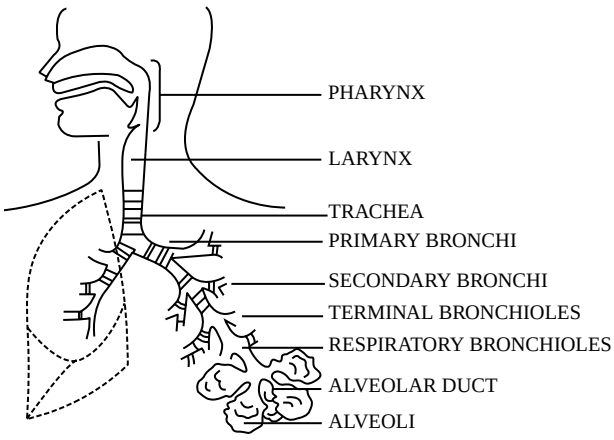

Fig. 1 The human respiratory tract.

reported with a pressurized metered-dose inhaler (6). Despite these advances, drug delivery via the lung is still inefficient.

Systemic availability of inhaled drugs may be inhibited by first-pass pulmonary metabolism. The lungs contain many drug metabolizing enzymes, including mixed function oxidases, monoamine oxidase, and esterases.

Several animal models principally the rat, rabbit, and dog, are used to study drug inhalation.

Intraperitoneal

Intraperitoneal drug administration is not common. It is used pedominantly to administer compounds during preclinical discovery and development. Its clinical use is generally limited to chemotherapy for tumors with peritoneal involvement.

Peritonitis occurs frequently in renally impaired patients who are receiving continuous ambulatory peritoneal dialysis (CAPD). Peritonitis is often accompanied by systemic infection so that therapeutic levels of antibiotic are needed both in the peritoneal cavity and in the systemic circulation.

Drugs may be given orally or by injection in order to achieve adequate systemic levels in the hope of also achieving therapeutic levels in the peritoneal cavity. Alternatively, drugs may be administered directly into the peritoneal cavity with the objective of also achieving systemic levels by intraperitoneal absorption (7). To the author's knowledge, there is little definitive information on the relative merits of these alternatives.

Vaginal

The human vagina, a fibromuscular tube 10–15 cm long, extends upwards and backwards from the vulva to the lower uterine cervix. Blood is supplied to the vagina via the uterine and pudendal arteries, and is drained from the vagina by a rich plexus, which flows into the internal iliac veins. The surface of the vaginal epithelium is kept moist by cervical secretions. The pH of vaginal fluid is 4–5.

Vaginal drug delivery is used mostly for local effects, but vaginal absorption can give rise to rapid and efficient systemic delivery. Good systemic absorption, and also the ability of the vagina to retain delivery devices, has given rise to many vaginal dosage forms, in particular for steroid contraceptives. A large number of vaginal controlled release dosage forms are available, including vaginal rings and biodegradable microspheres.

Rectal

The human rectum is 15–20 cm long. It is normally empty and contains 2–3 ml of mucous fluid with pH 7–8. There are no villi and only a limited surface area of 200–400 cm^2 is available for absorption.

Blood and lymph vessels are abundant in the rectal submucosa. Veins from the upper rectum drain into the portal circulation, while veins from the middle and lower rectum drain directly into the inferior vena cava. However, there are extensive anastomoses among these veins so that precise anatomical differentiation is difficult. It appears that compounds absorbed from the lower rectum, in contrast to those absorbed from the upper rectum, avoid hepatic first-pass metabolism.

Rectal absorption is generally slower than oral absorption, but for some drugs, rectal absorption exceeds oral absorption presumably due to avoidance of first-pass metabolism after rectal delivery. This has been reported for morphine, metoclopramide, ergotamine, lidocaine, and propranolol. Human rectal systemic availability of the extensively metabolized drug lidocaine is 65% as compared to 30% after oral administration (8).

Rectal absorption of drugs from aqueous or alcoholic solutions is generally much faster than from suppositories. Nonsurfactant adjuvants, such as salicylates, increase rectal absorption of water-soluble drugs and also of high molecular weight compounds, such as insulin, heparin, and gastrin.

ENTERAL ROUTES

Enteral routes of drug absorption are from the stomach and the small and large intestine. Substances absorbed from these areas enter the splanchnic circulation and pass through the liver before entering the systemic circulation.

The GI tract is the site of absorption for most nutrients. Thus, the GI tract has evolved to facilitate absorption of substances. The peristaltic action of the stomach, secretion of enzymes and hydrochloric acid, the villi and microvilli of the intestine, as well as the rich blood supply and lymphatics in this region, all facilitate absorption. Enteral absorption is generally by far the most effective drug delivery route and, whenever possible, drugs are administered in this way.

Any orally absorbed compound is exposed to an absorption environment that is both friendly and hostile, depending on the compound and the patient. A brief review of the structure and physiology of the GI tract relative to drug absorption follows.

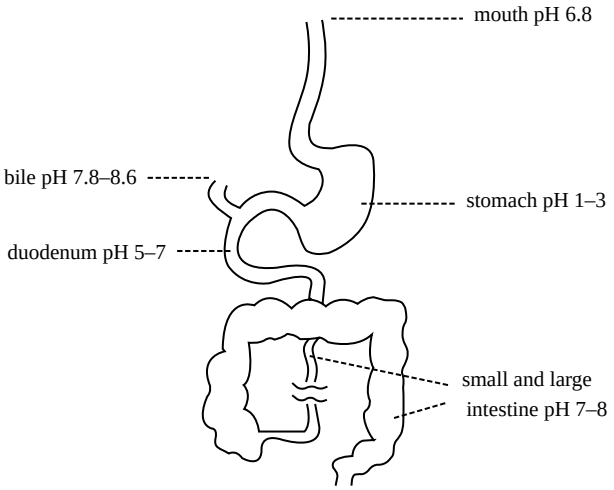

Fig. 2 Approximate pH values in the human gastrointestinal tract.

Physiology of the GI Tract

Figure 2 shows the pH of various regions of the GI tract. From the slightly acidic region of the mouth, a compound enters the more acidic region of the stomach. Acidity is a consequence of hydrochloric acid secretion by the parietal cells of the stomach. This plays an important role in food digestion by facilitating conversion of pepsinogens and zymogens to active proteolytic enzymes.

The acidic environment in the stomach tends to favor gastric absorption of acidic drugs provided the drugs are in solution. On the other hand, basic drugs tend to dissolve readily in the stomach but absorption may be prevented because the drug will be ionized and therefore not sufficiently fat soluble for efficient membrane penetration. The acidic environment in the stomach may give rise to reduced drug absorption due to acid-catalyzed degradation.

If a drug dissolves in the stomach or is a liquid, and if it is fat-soluble and acid stable, then it is likely to be absorbed efficiently from the stomach. Ethyl alcohol is a liquid that is completely miscible with water and sufficiently lipophilic to cross biological membranes. It is efficiently absorbed from the stomach.

After passing through the pyloric sphincter, a compound reaches the duodenum, jejunum, and ileum. These regions of the small intestine differ from the stomach with respect to pH, the presence of digestive enzymes, and the absorptive surface area. Excretion of alkaline bile into the duodenum raises the pH of the duodenal and more distal intestinal contents to 5–7. The change in pH from acidic to essentially neutral causes many changes that affect drug absorption. Enteric coatings that were impermeable in the stomach will dissolve. Acidic drugs will dissolve more rapidly and yet the pH will not be sufficiently high to prevent dissolution or cause precipitation of weakly basic drugs.

GI Structure and Motility

The stomach is a pouch-like organ lined with a relatively smooth epithelial surface. Although compounds can be absorbed from the stomach, the contribution of this organ to overall enteral drug absorption is modest. The absorptive properties of the proximal small intestine are superior to those of the stomach or any other region of the GI tract. The rate at which compounds pass from the stomach into the small intestine is a rate-limiting step controlling drug absorption. Stomach motility is complex and is influenced by nervous and hormonal stimuli. Stomach emptying rate is a function of rhythmic contractions that have a frequency of approximately three per minute in a fasted person, and less when food enters the stomach.

Food passes from the stomach into the duodenum as a result of these rhythmic contractions. The heavier the meal and the higher the fat content, the longer it will take for a meal, and any drug that may be ingested with it, to pass into the small intestine. This process acts as a defense mechanism by which substances are prevented from entering the proximal small intestine and injuring the delicate absorptive surface of this region until they are reduced to a suitable consistency in the stomach.

Whereas solid food delays stomach emptying, liquids tend to accelerate the process. Acceleration results from activation of stretch receptors in the stomach wall. When the fluid is water, activation of the inhibitory receptors is stopped. This results in rapid emptying of stomach contents into the duodenum.

By far the most important difference between the proximal small intestine and the stomach is the nature of the mucosal surface of the epithelium. The mucosal surface of the small intestine is increased by finger-like projections, or villi, that arise from the folds of Kerckring, and in turn by microvilli that arise from the villi. These invaginations increase the surface area of the intestinal mucosa some 600-fold to approximately 200 m^2, and 1.0–1.5 L of blood passes through intestinal capillaries each minute. Corresponding values for the stomach are only 100 m^2 of surface area and a blood flow rate of 150 ml/min. Thus, the small intestine has a surface area approximately double that of the stomach and a blood perfusion rate 6–10 times faster. Both factors strongly favor more efficient absorption from the small intestine.

The villi and microvilli of the small intestine are lined by a sulphated mucoprotein, glycocalyx. Fluid trapped within the glycocalyx is stationary, and a series of thin layers, each progressively more stirred, extends to the bulk phase of the intestinal lumen. This series of unstirred layers has an effective thickness of 0.01–1.0 mm.

Molecules move within the unstirred layers by diffusion at a rate inversely proportional to the square root of molecular weight below 450, and inversely proportional to the cube root of molecular weight above 450. The glycocalyx is negatively charged, with counterions in the unstirred layer. If a substantial proportion of these cations is composed of hydrogen ions, as is often the case, then the microclimate within the brush border of the epithelium is likely to be acidic relative to the bulk phase. This may influence drug ionization at the membrane surface, and provides a basis for the "acid microclimate" frequently associated with the GI mucosa.

The length of time during which material stays in the small intestine is approximately 5 min in the duodenum, 2 h in the jejunum, and 3–6 h in the ileum. Material then enters the large intestine.

The large intestine does not have villi or microvilli at its mucosal surface. Its contents are neutral or alkaline. Therefore, absorption of drugs from the large intestine is less efficient than from the small intestine. The large intestine and colon contain an active bacterial microflora that can degrade foreign molecules that also tends to reduce absorption of drugs from this region of the GI tract.

GI Secretions

The rate of acid secretion into the stomach is controlled by parietal cells. Acetylcholine, histamine, and gastrin are important for regulation of hydrochloric acid secretion, and they act directly on parietal cells to enhance acid secretion rate.

Phases of gastric acid secretion

The basal rate of hydrochloric acid secretion varies diurnally, being highest in the evening and lowest in the morning. After ingestion of a meal, the rate of acid secretion in the stomach increases. The three phases of increased acid secretion in response to food are the cephalic phase (before food reaches the stomach), the gastric phase (elicited by the presence of food in the stomach), and the intestinal phase (elicited by input from the duodenum and upper jejunum).

Cephalic phase

The sight, smell, and taste of food elicit this phase. Acid secretion during this phase can be as much as 40% of the maximum rate. Other stimuli sensed in the brain, in addition to those related to the presence of food, may evoke acid secretion through vagal impulses.

Gastric phase

The presence of food in the stomach evokes gastric secretion. The principal stimuli include distension of the stomach and the presence of amino acids and peptides. Distension of the stomach stimulates mechanoreceptors that bring about secretion of acetylcholine, hydrochloric acid, and gastrin.

Intestinal phase

The presence of chyme in the duodenum stimulates neuronal and endocrine responses that stimulate and later inhibit secretion of acid into the stomach. The stimulatory influences dominate when the pH of gastric chyme is above 3. However, when the buffer capacity is exhausted and the pH falls below 2, inhibitory influences dominate.

Gastric acid secretion may be regulated by several brain peptides, some of which may enhance secretion, while others may act centrally to inhibit secretion.

Gastric Juice

Gastric juice contains a mixture of secretions from surface epithelial cells and gastric glands. Salts, water, pepsins, intrinsic factor, and mucus are main components of gastric juice. Gastric secretions increase after a meal. Ionic composition of gastric juice is related to the rate of secretion. The higher the secretory rate, the higher the hydrogen ion concentration.. The rate of gastric acid secretion varies among individuals. In humans, the basal rate is 1–5 mEq/h. With histamine or pentagastrin stimulation, acid output rises to 5–40 mEq/h.

Other Secretions

Bile, pH 7.8–8.6, is produced continuously in humans. Hepatic bile is concentrated and stored in the gall bladder between meals. It is ejected from the gall bladder and flows into the duodenum when food enters the intestine. The main constituents of bile are bile salts, bilirubin, end products of hemoglobin breakdown, the electrolytes sodium, chloride, and bicarbonate, cholesterol, phospholipids, and lecithin. The gall bladder contracts within 30 min after eating due to liberation of cholecystokinin. The most effective stimulus to this is food high in fat.

Bile salts, which are surface active, promote dissolution of lipophilic drugs and lipophilic drug formulations, enteric coatings, and waxy drug matrices. Bile salts may

also promote membrane permeability of lipophilic molecules through micelle formation and solubilization.

Pancreatic juice contains an alkaline fluid and enzymes, both of which empty into the duodenum. The alkaline pH contributes to neutralization of the acid that empties from the stomach. The enzymes amylase, lipase, trypsin, and chymotrypsin play major roles in the digestion of carbohydrates, fats, and proteins. Trypsin and chymotrypsin are secreted as inactive precursors and are converted to the active forms enzymatically.

As a result of proteolytic enzyme secretion into the duodenum, protein or peptide drugs, such as corticotropin, vasopressin, and insulin, are rapidly degraded and generally cannot be given orally. Secretory activity of the pancreas is under hormonal and neuronal control.

Intestinal secretions do not exist in the same sense as gastric, pancreatic, or biliary secretions. Nonetheless, large fluid fluxes take place throughout the intestine. Any secretions from the intestinal mucosa appear to have a lubricant and protective effect.

GI Blood Flow in Relation to Drug Absorption

Drugs may be transported away from the serosal side of the GI tract by one or both of two mechanisms. The GI tract is supplied by a blood capillary network from the splanchnic circulation. Drugs may also be taken up by the lymph vessels in the GI epithelium and carried by the lymphatic system that drains the abdominal area into the thoracic duct. Any drug that is absorbed via this system enters the systemic circulation directly and is not susceptible to first-pass hepatic metabolism. Despite the presence of both the blood capillary network and the lymphatic system, absorption of the great majority of drugs appears to occur predominantly via the capillary system associated with the splanchnic circulation.

The reason for this appears to lie in the relative flow rates of blood and lymph. The rate of blood flow in the splanchnic circulation is 1.0–1.5 L/min, or 30% of cardiac output. This rate may increase to 2 L/min after a meal. Lymph flow through the same region is only 1–2 ml/min, but may increase to 5–20 ml/min after a meal. Lymph flow in this region is thus 500–700 times slower than blood flow. Relatively fast splanchnic blood flow establishes virtual sink conditions on the serosal side of the GI epithelium and ensures a steep concentration gradient. These conditions promote efficient absorption into the bloodstream rather than into lymph.

Only a small number of drugs are absorbed via the lymph system. These include drugs with high molecular weights that cannot enter the capillaries and specific molecules such as steroids.

Hepatic First-Pass Metabolism

The majority of compounds absorbed from the stomach and intestines enter the splanchnic circulation. This leads to the portal vein, the liver, and then to the general circulation. Compounds absorbed via this route must therefore pass through the liver and will do so initially at a higher concentration relative to when they eventually distribute into the general circulation and elsewhere.

As hepatic metabolism is generally first order in nature, a large proportion of any orally administered drug that is highly and efficiently metabolized in the liver will be cleared during the initial first pass. A drug could be efficiently absorbed from the GI tract and yet poorly available to the general circulation as a consequence of first-pass hepatic clearance. Such high extraction drugs include acebutolol, alprenolol, desipramine, isoproterenol, and lidocaine.

ABSORPTION MECHANISMS

An orally administered drug must pass through a number of membranes in order to be absorbed into the systemic circulation. Many physiological membranes differ in structure and function. Despite this, there is general consensus regarding the basic structure of the cell membrane.

The Cell Membrane

The primary structure of the cell membrane, shown in Fig. 3 (9) is a 5-nm thick bimolecular lipid film that separates intracellular and extracellular fluids. The lipid is composed mainly of the phospholipids phosphatidylserine and phosphatidylinositol, and contains saturated and unsaturated fatty acids and sterols. The bilayer exhibits high permeability to hydrophobic molecules and low permeability to hydrophilic molecules.

The cell membrane is associated with intrinsic and extrinsic proteins. Intrinsic proteins are globular proteins that generally span the bilayer and are held within the membrane by hydrophobic and electrostatic interactions. The proteins can form channels, carriers, or pumps that enable polar molecules to cross the membrane.

Membrane Transport

Several mechanisms have been identified for drug transport across membranes. One of them is passive. The remainder utilize some type of carrier mechanism.

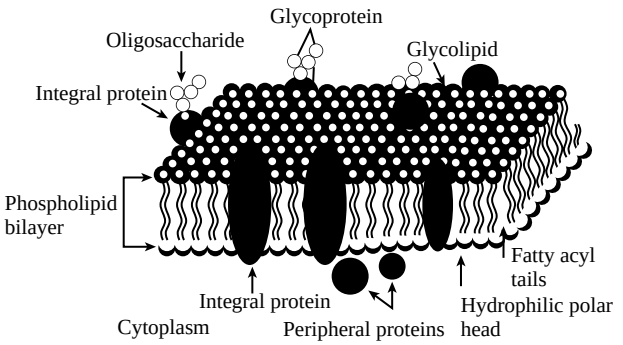

Fig. 3 Structural model of the cell membrane. The membrane is composed of a bimolecular leaflet of phospholipid with the polar head groups facing the extracellular and cytosolic compartments and the acyl groups in the middle of the bilayer. Integral membrane proteins are embedded in the lipid bilayer. Integral proteins are glycosylated on the exterior surface and may be phosphorylated on the cytoplasmic surface. Extrinsic membrane proteins, peripheral proteins, are linked to the cytosolic surface of the intrinsic proteins by electrostatic interactions. (From Ref. 9.)

Simple or Passive Membrane Transport

This mechanism, based primarily on lipid solubility and concentration gradient, is responsible for membrane transport of the great majority of drugs. The range of membrane permeabilities is very high. Typically, hydrophobic molecules have high partition coefficients, while hydrophilic molecules have low partition coefficients. The direction and rate of transport are determined by the concentration gradient of a substance across the membrane.

Molecules that are weak acids or bases cross membranes more readily when they are in the nonionized form. However, aqueous solubility is favored for the ionized form. In order to be available to cross any membrane, a drug must be in solution. This paradoxical requirement of both aqueous and lipid solubility is of particular concern in the area of drug absorption and presents a constant challenge in pharmaceutical formulation.

Transport Proteins

Many substances, particularly polar molecules, cross membranes at rates greater than those predicted from solubility and permeability data. Some can cross membranes against a concentration gradient. Unexpectedly high membrane permeability is related to transport proteins. Many transport proteins have been identified, cloned, and sequenced. Current knowledge has permitted an operational definition of carrier proteins as channels, carriers, and pumps. The current state of the art in identification and characterization of these systems has been described by Wright (9).

Channels

Initial speculation on the existence of small aqueous pores in membranes was based on high membrane permeability of small polar molecules. For example, the permeability of water is 1000-fold more, and that of urea 10- to 100-fold more, than predicted. These types of observations led to the prediction of aqueous channels with radii of approximately 4 Å.

Water channels

The presence of water channels has been demonstrated by successful cloning of proteins that increase membrane water permeability. These have been expressed in erythrocytes and in cells of the renal tubule.

Ion channels

Evidence for ion channels in biological membranes was introduced in the 1970s. Possibly the most significant experiment was by Neher and Sakmann (10), who recorded single ion channel currents in muscle fibers. Many types of channels for sodium, potassium, calcium, and chloride ions have been described, and each has a specific conductance, ion selectivity, and probability of opening. Ion channel opening may be controlled by voltage or by ligand, and channels are thus designated voltage-gated or ligand-gated. Each of the ion channels has a specific pharmacology. Sodium channels are 12 times more selective for sodium than for other cations. Calcium channels are 1000 times more selective for calcium than for other cations.

Facilitated Diffusion

Facilitated diffusion is a simple mechanism proposed to explain transport of water soluble compounds. The main characteristics of this transport system are that membrane permeability exceeds that predicted from partition coefficients, transport occurs down a concentration gradient, transport is saturable, and competition occurs between isomers. Facilitated diffusion has been used to explain cellular uptake of sugars and amino acids.

Six human sugar transporters with different tissue distributions, substrate kinetics, and specificities have been identified. A number of facilitated amino acid transporters have also been identified in mammalian cells. System L,

which transports neutral amino acids, such as leucine and phenylalanine, is probably the best known of these.

Pumps

Pumps are proteins that can transport ions against electrochemical potential gradients using adenosine-5-triphosphate (ATP) as an energy source. Sodium–potassium pumps maintain intracellular sodium and potassium concentrations in animal cells and also control salt and water absorption by the epithelial cells in the intestine and kidney. The sodium–potassium pump transports three sodium ions out of the cell and two potassium ions into the cell at the cost of one molecule of ATP. The 3:2 coupling ratio results in net loss of sodium ions into the cell down an electrochemical gradient and maintains cell volume. Currently, considerable research is attempting to elucidate the structures of the various isoforms and subunits of sodium potassium pumps.

Cotransporters and Exchangers

There are many other examples of ions and ionized molecules accumulating in cells against their concentation gradient, such as uptake of iodine by the thyroid gland, accumulation of acids in liver cells, and absorption of sugars and phosphate by the small intestine. Recent studies have shown that these are governed by cotransport mechanisms. In all cases tested to date, sodium or hydrogen ion gradients are used to drive cotransporters, and these gradients are maintained by ion pumps. Glucose transport across the brush border of the small intestine is coupled with sodium transport, and uphill sugar transport is driven by the sodium gradient.

Cotransporters

Cotransporters use the sodium or hydrogen ion gradient to drive transport of a substrate. Many cotransporters have been described, cloned, sequenced, and expressed. The sodium–glucose cotransporter just described is one of these.

Other cotransporters facilitate the transport of other sugars, osmolytes, and amino acids. In humans, a disorder of intestinal glucose and galactose absorption is due to a defective sodium–glucose transporter.

Antiporters

The best characterized antiporters, or exchangers, are the chloride–bicarbonate, sodium–hydrogen ion, and sodium–calcium exchangers. The cellular sodium-hydrogen ion exchanger controls cell volume, pH, growth, and sodium transport. Mammalian isoforms of these exchangers have been cloned and sequenced. Sodium-hydrogen exchangers play a dominant role in the regulation of intracellular calcium, and thus the force of contraction of the heart. The therapeutic effect of cardiac glycosides is probably related to decreased sodium-calcium exchange in the heart caused by a decreased sodium–hydrogen gradient across the cell membrane.

Permeability Glycoprotein

Permeability glycoprotein (p-glycoprotein) is an ATP-dependent efflux pump responsible for pumping substances out of cells. It is implicated in development of drug resistance in tumor cells. Localization of p-glycoprotein in the apical membranes of intestinal, liver, and kidney cells, and also at the blood brain barrier, provides potential for this pump to have a profound effect on drug absorption, distribution, and elimination, as well as in drug–drug interactions.

Pinocytosis and Endocytosis

Pinocytosis is a nonspecific process whereby a substrate enters a cell by invagination to form an intracellular vesicle. Receptor-mediated endocytosis occurs when substrate binds to a specific membrane receptor. Substrates ingested by cells in this way are stored in vesicles or degraded. Receptor-mediated endocytosis is involved in cellular uptake of immunoglobulin and low density lipoprotein.

FORMULATION FACTORS AFFECTING DRUG ABSORPTION AND ABSORPTION ENHANCERS

The chemical and physical properties of a drug and its formulation can affect drug stability and absorption characteristics.

Chemical Factors

A variety of chemical options can be used to improve the stability and systemic availability of drugs. For example, esters can be prepared of both acids and bases to produce more stable derivatives, which hydrolyse to the active parent once absorbed. The stability and solubility of both acids and bases tend to increase when they are in the form of salts. Typically, administration of soluble salts of penicillin give rise to higher circulating antibiotic levels

than the free acid. When the salt of a weak acid dissolves in the stomach, it generates a diffusion layer of relatively high pH which, in turn, promotes further dissolution. The same argument could theoretically be used for basic drugs. However, the pH effect in this case is swamped by the very low pH present in stomach fluids. Thus, salts of basic drugs are used primarily for handling and solubility rather than for improved dissolution.

Physical Factors

Different physical forms of a drug can affect its absorption. Typically, the crystal or polymorphic form, the state or nature of hydration or solvation, and physical size of drug particles may have considerable impact on the rate and extent of drug absorption.

Polymorphism and amorphism

Many compounds form crystals with different molecular arrangements, or polymorphs. These polymorphs may have different physical properties, such as dissolution rate and solubility. The vitamin riboflavin exists in several polymorphic forms, and these have a 20-fold range in aqueous solubility. Polymorphs that have no crystal structure, or amorphic forms, have different physical properties from the crystalline forms.

Absorption of many orally administered drugs is controlled by dissolution rate. Amorphous forms generally dissolve faster than crystalline forms because no energy is needed to break up the crystal lattice. For this reason, the amorphous form is often preferred over the crystalline form and several drugs, including hydrocortisone and prednisolone, are marketed in the amorphic form.

Solvation

During their preparation, drug crystals may incorporate one or more solvent molecules to form solvates. The most common solvate is water. If water molecules are already present in a crystal structure, the tendency of the crystal to attract additional water to initiate the dissolution process is reduced, and solvated (hydrated) crystals tend to dissolve more slowly than anhydrous forms. Significant differences have been reported in the dissolution rate of hydrated and anhydrous forms of ampicillin, caffeine, theophylline, glutethimide, and mercaptopurine. The clinical significance of these differences has not been examined but is likely to be slight.

Particle size

Particle size may play a major role in drug absorption. Dissolution rate of solid particles is proportional to surface area, and hence to particle fineness. Particle size reduction has been used to increase the absorption of a large number of poorly soluble drugs, such as bishydroxycoumarin, digoxin, griseofulvin, nitrofurantoin, and tolbutamide.

Griseofulvin has extremely low aqueous solubility, and material of normal particle size gave rise to poor and erratic absorption. Microsize particles improve absorption, but it is improved even more when it is formulated in ultramicrosize particles as a monomolecular dispersion in polyethylene glycol.

Formulation Factors

Drug formulations are designed to provide an attractive, stable, and convenient method to use products. Conventional dosage forms may be broadly characterized in order of decreasing dissolution rate as solutions, solid solutions, suspensions, capsules and tablets, coated capsules and tablets, and controlled release formulations.

Solutions

Aqueous solutions, syrups, elixirs, and emulsions do not present a dissolution problem and generally result in fast and often complete absorption as compared to solid dosage forms. Due to their generally good systemic availability, solutions are frequently used as bioavailability standards against which other dosage forms are compared.

Solid solutions

The solid solution is a formulation in which drug is trapped as a solid solution or monomolecular dispersion in a water-soluble matrix. Although the solid solution is an attractive approach to increase drug absorption, only one drug, griseofulvin, is currently marketed in this form.

Suspensions

A drug in a suspension is in solid form, but is finely divided and has a large surface area. Drug particles can diffuse readily between the stomach and small intestine so that absorption is relatively insensitive to stomach emptying rate.

Similar to solutions, suspensions are useful for patients who have difficulty taking solid medication. Adjusting the dose to a patient's needs is easier with solutions and suspensions than with solid dosage forms. Liquid dosage forms, therefore, have several practical advantages besides simple dissolution rate. However, they also have some disadvantages, including greater bulk, difficulty in handling, and perhaps reduced stability.

Capsules and tablets

Capsules and tablets are the most common oral dosage forms. These formulations differ from each other in that material in capsules is less impacted than in compressed tablets. Once a capsule dissolves, the contents generally disperse quickly. The capsule material, although water soluble, can impede drug dissolution by interacting with the drug, but this is uncommon.

Tablets generally disintegrate in stages, first into granules and then into primary particles. As particle size decreases, dissolution rate increases due to of increased surface area.

Tablet disintegration was once considered a sufficient criterion to predict in vivo absorption. This was proven inadequate, however, and dissolution is now recognized as a better criterion. Regulatory agencies now require dissolution rate data for all new oral formulations. The increasingly wide acceptance of dissolution as the best available in vitro parameter to predict in vivo absorption is reflected in the proliferation of such tests in official compendia.

Excipients: Along with active material contained in tablets and capsules, a variety of so-called inert ingredients are present, for example, starch, magnesium aluminum silicate, methylcellulose, carboxymethylcellulose, lactose, kaolin, talc, calcium sulfate, and magnesium stearate. Tablets may also have a variety of coatings to improve stability, taste, appearance, and drug release characteristics. Although considered to be inert, these additives can affect drug dissolution and absorption. Changing an excipient from calcium sulfate to lactose and increasing the proportion of magnesium silicate, increases the activity of oral phenytoin. Systemic availability of thiamine and riboflavin is reduced by the presence of Fuller's earth. Absorption of tetracycline from capsules is reduced by calcium phosphate due to complexation.

Most of these types of interactions were reported some time ago and are unlikely to occur in the current environment of rigorous testing of new dosage forms and formulations.

Coated tablets

Tablets may be formulated with coatings such as shellac, resin, or styrene-maleic acid copolymer. These coatings are insoluble in acid but dissolve readily at neutral or alkaline pH. Thus they are ideally suited to prevent drug release until the formulation has passed from the stomach into the small intestine. Preventing drug release in the stomach may protect drugs that are acid labile. It may also protect the patient from irritant substances like iron salts, diethylstilboestrol, and some anti-inflammatory agents. Release, and subsequent systemic availability of drugs from these formulations is likely to be highly sensitive to stomach emptying patterns.

In vitro–in vivo correlations: The relationship between in vitro dissolution and in vivo bioavailability is of considerable interest today. The U.S. Food and Drug Administration (US FDA) has spearheaded a research program to examine these relationships with the objectives to gain a better understanding of their interdependence and to use the relationships as a means to predict in vivo performance from in vitro data. The cost savings of realization of this second objective would be significant. The main thrust of research in this area is based on differentiation of drugs or formulations in terms of solubility and membrane permeability (11).

Drugs or formulations can be considered in four groups: 1) high solubility and low permeability; 2) high solubility and high permeability; 3) low solubility and high permeability and 4) low solubility and low permeability. For drugs in group 3, dissolution is likely to be rate-limiting for absorption and in vitro dissolution data may be useful. For drugs in group 1, on the other hand, permeability is probably rate-limiting and in vitro data are less likely to be useful. For groups 2 and 4, the picture is less clear and in vitro–in vivo relationships would need to be determined experimentally.

Controlled release formulations

Appreciation of the advantages of controlled drug release, development of many novel controlled release systems, and also the interest of major pharmaceutical houses in protecting marketed drug products, have led to increased interest in this type of dosage form. Most controlled release products currently marketed include diuretic agents, cardiovascular and respiratory drugs, and compounds acting on the CNS. Little attention has been paid to antimicrobial agents.

Advantages of controlled drug release: Due to of their generally higher cost, controlled release dosage forms can be justified only if they offer therapeutic advantages, i.e., improved maintenance of therapeutic drug levels in the circulation, reduced dosing frequency, reduced fluctuation in circulating drug levels, increased convenience to the patient, reduced patient care time, less nighttime dosing, more uniform pharmacologic response, reduced GI irritation, and reduced side effects. The second of these, reduced dosing frequency, has often been claimed as a sufficient rationale for development of a controlled release dosage form, but has become unacceptable as a sole criterion. This is understandable given the current emphasis on cost containment in health care.

Disadvantages of controlled drug release: Potential disadvantages of controlled release dosage forms include the possibility of dose dumping, less facile dose adjustment, increased potential for hepatic first-pass metabolism, possible delay in onset of action, possibly lower system availability, and time of drug release limited to residence time of formulation in the optimum absorption region(s) of GI tract.

Dose dumping, or inadvertent rapid release of drug, is important for potent drugs that have a narrow therapeutic index. Good manufacturing practice (GMP) generally reduces the probability of this happening. Fine dose adjustment is often difficult with controlled release formulations. Controlled release tablets that use a granule matrix may be subdivided in order to reduce the dose, but repeat action tablets or osmotic pump devices lose their controlled release properties once the dosage form is fractured. Increased first-pass metabolism may occur with drugs that are cleared by the liver, but only if hepatic clearance is saturable following rapid absorption from conventional dosage forms. Reduced systemic availability is common with controlled release dosage form, availability generally being 80–85% of that from conventional formulations. Limited residence time in the GI tract is a potential disadvantage of oral controlled release products, and this distinguishes oral from other controlled release dosage forms (e.g., skin patches, which can provide slow release of drug over a prolonged period).

Drugs that are unsuitable for controlled release: Some drugs are unsuitable for controlled release formulations. Typical characteristics of such drugs include short biological half-life, long biological half-life, potent drug with narrow therapeutic index, large dose, poorly absorbed, low or slow dissolution, active absorption, time course of activity not the same as that of circulating drug levels, and extensive first-pass metabolism.

A controlled release form of a drug that has a short biological half-life, <2 h, or is administered in large doses may need to contain a prohibitively large amount of drug. Drugs with long biological half-lives (>8 h) are generally sufficiently sustained in the body from conventional doses, and prolonged release is unnecessary. Incorporating slowly dissolving compounds into a controlled release formulation is likely to be counterproductive since dissolution is rate-limiting anyway. Administering drugs like warfarin, whose pharmacologic effect is prolonged relative to its blood profile, offers no therapeutic advantage. Incorporating such compounds as some beta-lactam antibiotics, fluorouracil, and some amino acids, which appear to be absorbed predominantly from the proximal intestine, is likely to reduce their efficacy and achieve little or no prolongation of effect. As stated earlier, if a drug undergoes saturable first-pass metabolism from conventional doses, its systemic availability may be decreased after controlled release.

Although the above arguments provide useful general rules, there are many exceptions. Nitroglycerin has a biological half-life of less than 0.5 h. It is generally considered to be poorly absorbed and is rapidly metabolized by the liver, with obvious first-pass implications. However, a large number of oral controlled nitroglycerin products are marketed. Low circulating levels of nitroglycerin obtained from these products appear to provide adequate prophylaxis against angina attacks, but not against acute angina episodes. Some established and more recently introduced controlled release dosage forms are given in Table 1 (12).

Absorption Enhancers

Although oral dosing is generally more convenient than other dosage routes, oral absorption of many drugs is poor. As molecules become larger, more complex, and generally more lipophilic in the quest for new or improved efficacy, their absorption tends to decline. To address this problem, absorption enhancers continue to be examined, so far with variable success. Some compounds that have been shown, largely in animal studies, to increase absorption of drugs are shown in Table 2 (13). Little or no information is available in humans for most of these compounds.

Nonsteroidal antiinflammatory agents (NSAIDs)

NSAIDs, in particular indomethacin, diclofenac, mepirazole, phenylbutazone, and salicylate, can promote absorption of other drugs, including insulin, ampicillin, cephalothin, cefoxitin, and cefmetazole. Most of these observations were made in the rat and frequently after rectal administration. Several mechanisms by which NSAIDs promote drug absorption have been postulated, but exact mechanisms are not known. As NSAIDs are often irritating to the GI mucosa, and this may well relate to their absorption enhancing ability, the feasibility of their use to promote drug absorption is uncertain.

Surfactants

In view of their solubilizing effects and also their potential to change membrane permeability, surfactants have been considered as absorption enhancers, again mostly in animals. Polyoxyethylene ethers have been shown to enhance gastric or rectal absorption of lincomycin, penicillin, cephalosporins, and fosfomycin in rats and

Table 1 Some oral controlled-release dosage forms

Category	Product	Active ingredient
Slow erosion with initial fast release dose	Tedral SA	Theophylline, ephedrine, phenobarbital
Erosion core only	Tenuate Dospan	Diethylpropion
Repeat action tablets	Chlor-trimeton repetabs	Pseudoephedrine, chlorpheniramine
Pellets in capsules	Combid spansule	Isopropamide, prochlorperazine
Pellets in tablets	Theo Dur	Theophylline
Leaching	Desbutal gradumet	Methamphetamine, pentoparbital
Ion exchange resin	Biphetamine	Amphetamine, Dextroamphetamine
Complexation	Rynata	Chlorpheniramine, phenylephrine, pyrilamine
Microencapsulation	Nitrospan	Nitroglycerin
Flotation–diffusion	Valrelease	Diazepam
Osmotic pump	Acutrim	Phenylpropanolamine
	ProcardiaXL	Nifedipine

(From Ref. 12.)

rabbits. In rats, colonic absorption of interferon–alpha is increased from 3 to 8% by polyoxyethylene esters of oleic acid and oleic acid glycerides.

Some studies have examined the effects of surfactants on intestinal absorption of insulin, with variable results. Both rectal and jejunal absorption of insulin was increased by anionic and cationic surfactants. However, in humans, oral polyoxyethylene-20-oleyl ether resulted in poor and variable insulin absorption (14).

Any enhancing effect of surfactants on drug absorption appears to be related to increased drug solubilization, modification of mucosal permeability, or reduction of resistance of the unstirred water layer at the GI membrane surface. In general, unionic surfactants have little effect on membrane structure but cationic surfactants have been associated with reversible cell loss and loss of goblet cells. These effects must limit consideration of surfactants as absorption promoters, particularly for long term treatment.

Table 2 Some types of oral drug absorption enhancers

Nonsteroidal antiInflammatory agents
Surfactants
Bile salts
Medium chain fatty acids
Mixed micelles
Liposomes
Azone
Cell permeation enhancers
Nanoparticles

(From Ref. 13.)

Bile salts

Bile contains conjugates of cholic acid and chenodeoxycholic acid, which emulsify dietary fat, facilitate lipolysis, and transport lipid molecules through the unstirred layer of the intestinal mucosa by micellar solubilization. The ability of bile salts to promote lipid absorption has prompted their investigation as absorption enhancers for drugs, with modest success. Studies in animals have demonstrated increased intestinal absorption of heparin and interferon-alpha. Absorption of insulin can be increased by bile salts, both in experimental animals and in humans. The effect on drug absorption appears to correlate with mucosal damage. This, together with possible cocarcinogenic and comutagenic properties of secondary bile salts, reduces the attractiveness of bile salts as absorption enhancers.

Medium-chain fatty acids and glycerides

The presence of medium chain fatty acids and glycerides in food products has stimulated interest in their potential utility as absorption enhancers. Some fatty acids and glycerides have been shown to increase drug absorption under a variety of conditions, almost always in animals and in most cases after rectal dosing. However, some studies have yielded positive results after oral dosing. Oral insulin bioavailability was increased to 9–13% relative to IM administration by a mixture of sodium dodecanoate and cetyl alcohol (15). Aftiraxone absorption was enhanced by glyceryl-1-monooctanoate after oral, duodenal, and rectal administration to animals.

Despite the potential of these classes of compounds as absorption enhancers, they have been shown to have negative effects on mucosal membrane integrity. Additional research is needed to evaluate risks and benefits.

Mixed micelles

Mixed micelles consist of fatty acids solubilized by surfactants or bile salts. The effects of mixed micelles on drug absorption were reviewed by Muranishi et al. (16). Mixed micelles are effective absorption enhancers for compounds such as heparin, streptomycin, gentamycin, and insulin. The effect of mixed micelles on drug absorption tends to be greater at the distal region of the GI tract. The mechanism for increased absorption is not known. Some publications claim that they are safe to use. Others report a disordering effect on intestinal epithelial cells.

Liposomes

Liposomes consist of vesicles composed of bilayers or multilayers that contain phospholipids and cholesterol surrounding an aqueous compartment. Drug is entrapped within the liposome and is released from the liposome for absorption at the intestinal membrane surface. This dosage form received considerable attention during the 1970s and 1980s, and several animal studies demonstrated potential for absorption enhancement. However, lack of effect in other studies, and also stability problems, have resulted in reduced interest in liposomes as absorption enhancers.

Azone

Azone (1-Dodecylazacycloheptan-2-one) and related compounds have been studied as transdermal penetration and oral absorption enhancers. Although some efficacy has been shown, an emulsifying agent appears to be necessary for azone to penetrate the intestinal mucosal membrane in order to promote drug absorption. One study reported the absence of gross morphological damage after exposure of mucosa to azone (17) but additional information on the effect of azone on overall mucosa structure is not avalable.

Cell permeation enhancers

Although the objective of most absorption enhancers is to avoid direct interaction with the mucosal membrane, cell permeation enhancers use this as a means to increase drug absorption. One form of enhancer currently of interest consists of glycosylated molecules, or facial amphiphiles. It is claimed that these compounds temporarily increase membrane permeability. Molecules are designed to self-assemble in membranes to form transient pores that permit hydrophilic compounds to cross the membrane. This technology has considerable potential for absorption enhancement. No adverse effects have been reported to date (18).

Nanoparticles

From known relationships between surface area and dissolution, it is reasonable to predict that ultrafine particles may increase the dissolution rate of relatively insoluble compounds. If these particles are then stabilized to avoid aggregation and agglomeration, and yet retain fluidity, then a useful drug product could be obtained.

This concept has found expression in a proprietary nanoparticle technology in which a drug is reduced to nanometer-size particles in the presence of stabilizers. Originally developed for IV computer imaging (19), this technology shows considerable promise to increase absorption of poorly water soluble compounds. As the nanoparticle system is purely "formulation" in nature, it is unlikely to affect GI mucosal integrity. Nanoparticles are sufficiently small that they can be used parenterally, apparently without ill effects. More is likely to be heard about this novel absorption enhancer technology.

CONCLUSIONS

The rate and extent of drug absorption into the systemic circulation are key factors that influence drug pharmacologic activity. Drugs may be administered by a variety of routes, each with its own advantages and disadvantages. The route of administration for a particular drug is dictated by the properties of the drug and the systemic activity profile required.

Increased knowledge of membrane structure and of transmembrane transport has improved understanding of the mechanisms of drug absorption and of ways in which this may be modulated.

Formulation continues to play a pivotal role in drug absorption. Many enhancer technologies have been examined, with varying success. However, some recent technologies based on formulation or membrane effects show considerable potential to increase absorption of orally administered compounds.

REFERENCES

1. Yamada, K.; Bremer, A.M.; West, C.R.; Ghoorah, J.; Park, H.C.; Takita, H. Intra-arterial BCNU Therapy in the Treatment of Metastatic Brain Tumor from Lung

Carcinoma. A Preliminary Report. Cancer **1979**, *44*, 2000–2007.
2. Goldman, J.A.; Peleg, D.; Agmon, M.; Shapiro, G. Arteriography and Chemotherapy in Localized Trophoblastic Disease by Means of Local-Pelvic-Intra-arterial Infusion. Acta Obstet. Gynecol. Scand. **1979**, *58*, 415–416.
3. Florence, A.T.; Jenkins, A.W.; Loveless, A.H. Approaches to the Formulation of a Long-acting Intramuscular Injection. J. Pharm. Pharmacol **1973**, *25* (Suppl.), 120–121.
4. Chandrasekaran, S.K. Controlled Release of Scopolamine for Prophylaxis of Motion Sickness. Drug Dev. Ind. Pharm **1983**, *9*, 627–646.
5. Su, K.S.E.; Campanale, K.M. Nasal Drug Delivery Systems Requirements, Development and Evaluations. *Transnasal Systemic Medications*; Chien, Y.W., Ed.; Elsevier Scientific: Amsterdam, 1985; 139–159.
6. Newman, S.P.; Miller, A.B.; Lennard-Jones, T.R.; Moren, E.; Clarke, S.W. Improvement of Pressurised Aerosol Deposition with Nebuhaler Space Device. Thorax. **1984**, *39*, 935–941.
7. Rogge, M.C.; Johnson, C.A.; Zimmermann, S.W.; Welling, P.G. Vancomycin Disposition During Continuous Ambulatory Peritoneal Dialysis: A Pharmacokinetic Analysis of Peritoneal Drug Transport. Antimcrob. Ag. Chemother. **1985**, *27*, 578–582.
8. Ritschel, W.A.; Elconin, H.; Alcorn, G.J.; Denson, D.D. First-pass Elimination of Lidocaine in the Rabbit after Peroral and Rectal of Administration. Biopharm. Drug Dispos. **1985**, *6*, 281–290.
9. Wright, E.M. Membrane Transport. *Pharmacokinetics: Regulatory, Industrial, and Academic Perspectives*, 2nd Ed., Welling, P.G., Tse, F.L.S., Eds.; Marcel Dekker, Inc.: New York, 1995; 89–118.
10. Neher, E.; Sakmann, B. Single-channel Currents Recorded from Membrane of Denervated Frog Muscle Fibres. Nature **1976**, *260*, 799–802.
11. Amidon, G.L.; Lennernas, H.; Shah, V.P.; Crison, J.R. A Theoretical Basis for a Biopharmaceutics Drug Classification: The Correlation of In Vitro Drug Product Dissolution and In Vivo Bioavailability. Pharm. Res. **1995**, *420*, 413–420.
12. Welling, P.G. Physicochemical and Formulation Factors Affecting Drug Absorption. *Pharmacokinetics: Processes, Mathematics, and Applications*, 2nd Ed., American Chemical Society: Washington, DC, 1997; 88.
13. van Hoogdalem, E.J.; de Boer, A.G.; Breimer, D.D. Intestinal Drug Absorption Enhancement. An Overview. Pharmacol. Ther. **1989**, *44*, 407–433.
14. Galloway, J.A.; Root, M.A. New Forms of Insulin. Diabetes **1972**, *21* (Suppl 2), 637–648.
15. Touitou, E.; Rubinstein, A.; Donbrow, M.; Azaz, E. New Hydrophilic Vehicle Enabling Rectal and Vaginal Absorption of Insulin, Heparin, Phenol Red and Gentamicin. J. Pharm. Pharmacol. **1978**, *30*, 662–663.
16. Muranishi, S. Modification of Intestinal Absorption of Drugs by Lipoidal Adjuvants. Pharm. Res. **1985**, *2*, 108–118.
17. Murakami, M.; Takado, K.; Muranashi, S. Promoting Effect of Azone on Intestinal Absorption of Poorly Absorbable Drugs in Rats. Int. J. Pharm. **1986**, *31*, 231–238.
18. Cheng, Y.; Ho, D.M.; Gottlieb, C.R.; Kahne, D. Facial Amphiphiles. J. Am. Chem. Soc. **1992**, *114*, 7319–7320.
19. Gazelle, G.S.; Wolf, G.L.; Bacon, E.R.; McIntire, G.L.; Cooper, E.R.; Toner, J.L. Nanocrystalline Computed Tomography Contrast Agents for Blood-Pool and Liver-Spleen Imaging. Invest. Radiol. **1994**, *29*, S268–S288.